Remarks

1. Status of the Claims

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 18-20, 22-41, and 43-71 are pending in the application, with claims 18 and 38 being the independent claims. Claims 21 and 42 are sought to be cancelled, without disclaimer to the subject matter therein. Claims 18 and 38 are sought to be amended. Support for the amendments to the claims is discussed in detail below. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

2. Summary of the Office Action

In the Office Action, the Examiner made one objection, four rejections, and one provisional nonstatutory obvious-type double patenting rejection to the claims. Applicants respectfully offer the following remarks concerning the objection, rejections, and provisional rejection.

3. Objection

At page 3, the Examiner has objected to claim 38 because of the following alleged informalities: "TFP" should be defined in the preamble and "mutant strain yeast" in (e) should read "yeast mutant strain" for consistency. As shown in the claim amendments filed herewith, claim 38 has been amended as suggested by the Examiner. Thus, Applicants respectfully request that the objection to claim 38 be reconsidered and withdrawn.

4. Rejection under 35 U.S.C. § 112 (Written Description)

"New Matter" Rejection

At pages 5, paragraphs 13-14 of the Office Action, the Examiner has rejected claims 18-20, 22-23, 25-34, and 38 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. In particular, the Examiner alleges that the phrase "one **or more** of said plurality of polynucleotide fragments comprises said TFP" (emphasis added) was not found in the originally filed specification. The Examiner states that this is a new matter rejection. Applicants respectfully traverse this rejection.

In an effort to advance prosecution, and not in acquiescence to the Examiner's rejection, part (b) of claims 18 and 38 has been amended to recite "linking a polynucleotide fragment to said automatic screening vector to create a library." Support for the amendments to part (b) of claims 18 and 38 can be found, *e.g.*, at page 14, lines 12-14; page 16, lines 3-13; page 47, line 17 to page 48, line 11; and original claim 1. Furthermore, part (e) of claims 18 and 38 has been amended to recite "identifying whether the polynucleotide fragment linked to said automatic screening vector comprises said TFP by detecting activity of said reporter protein which is secreted from one or more of said host cells." Support for the amendments to part (e) of claims 18 and 38 can be found, *e.g.*, at page 13, line 22 to page 14, line 17; page 49, line 14 to page 54, line 23; and original claim 1.

At page 5, paragraph 14 the Examiner asserts that "support was not found for more than one TFP linked to a single vector (see method step b of claims 18 and 38)." Applicants respectfully point out to the Examiner that the phrase "one or more of said plurality of polynucleotide fragments comprises said TFP" was not intended to refer to more than one TFP

linked to a single vector, as suggested in the Examiner's rejection. Instead the phrase "one or more of said plurality of polynucleotide fragments comprises said TFP" was intended to indicate that one or more polynucleotide fragments of (b) comprise a TFP, which is supported throughout the specification, *see, e.g.*, page 13, line 23 to page 24, line 20; and original claim 1. However, as indicated above, the phrase has been deleted from claims 18 and 38. Therefore, the Examiner's rejection is moot and Applicants respectfully request that the "new matter" rejection to be reconsidered and withdrawn.

"Written Description" Rejection

In addition, at pages 5-9, paragraph 15 of the Office Action, the Examiner has rejected claims 18-20, 22-23, 25-34, and 38 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. In particular, the Examiner alleges that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, the Examiner alleges that the invention encompasses all known TFPs and all potential TFPs. Office Action at page 6. The Examiner also alleges that the invention does not provide any structural information regarding the TFPs. Applicants respectfully traverse this rejection.

An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g.*, *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000) (the written description "inquiry is a factual one and must be assessed on a case-by-case basis"). Applicants

respectfully assert that the application as filed provides sufficient written description to *identify* a TFP using the claimed method of the invention.

The present invention is directed to a method for identifying a translational fusion partner (TFP) capable of stimulating the secretion of a non-producible target protein. Since the claims are directed to a method used to identify a TFP, not the TFPs themselves, knowledge of the structure of TFP is not essential to the claimed invention. In particular, a person of ordinary skill in the art would not need to know the particular structure of the TFP to use the claimed method.

Guidance related to creating a library of the invention which includes the candidate TFP(s) to be identified by the claimed method is disclosed in the specification, *e.g.*, at page 16, lines 3-13; page 18, lines 8-19. In addition, sufficient disclosure related to the definition of a "translation fusion partner (TFP)" to allow a person of ordinary skill in the art to use the claimed method to *identify* a TFP of the invention is provided in the specification as filed. *See, e.g.*, page 14, line 21 to page 15, line 1.

Applicants believe that claims 18 and 38, and claims 19-20, 22-23, 25-34, which ultimately depend from claim 18, are fully supported by the application as filed. Thus, Applicants respectfully request that the rejection to claims 18-20, 22-23, 25-34, and 38 be reconsidered and withdrawn.

5. Rejection under 35 U.S.C. § 112 (Indefinite)

At pages 9-10 of the Office Action, the Examiner has rejected claims 18-20, 22-23, 25-34, and 38 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter applicants regard as the invention. In particular, the Examiner asserts that a person of skill in the art would not be able to determine

the scope of the presently claimed invention, *e.g.*, the Examiner asserts that the metes and bounds of "which is poorly secreted by recombinant production" is not clear. Office Action page 10. Applicants respectfully traverse this rejection.

In an effort to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have amended claims 18 and 38, and provide the following comments.

First, Applicants respectfully assert that the phrase "a target protein which is poorly secreted by recombinant production" is not indefinite. In particular, not only does the specification particularly discloses properties of and methods for determining whether a protein is poorly secreted by recombinant production, the specification also discloses examples of proteins that are poorly secreted by recombinant production (*e.g.*, page 15, lines 2-22; page 16, line 14 to page 17, line 7; page 21, lines 19-25; page 22, line23 to page 23, line 9). For example, page 16, line 14-23 of the specification discloses that when a poorly secreted target protein is fused to a reporter protein, such as invertase, the secretion of the reporter protein from host cells is significantly inhibited. Furthermore, a working example disclosed in Example 2 (pages 43-46) demonstrates that the expression of invertase (an example of a reporter protein) was poor when fused to IL-2 (an example of a poorly-secreted target protein). Thus, a person of ordinary skill in the art would understand from the teaching of the present application the level of secretion of a target protein is considered poor.

However, not in acquiescence to the Examiner's assertion and solely to advance prosecution, claims 18 and 38 have been replaced the phrase "a target protein which is poorly secreted by recombinant production" with the pharase "a non-producible target protein." Furthermore, dependent claims 21 and 42 directed to a non-producible target protein have been cancelled. Because the term "a non-producible protein" is used throughout the specification

including to describe poorly secreted proteins, Applicants have amended the claim to include the term "a non-producible protein." The scope of the term "a non-producible protein" can be clearly derived from the specification as filed, including the disclosure at page 1, lines 8-10; page 8, lines 10-18; page 14, lines 21 to page 15, line 22; page 16, line 14 to page 17, line 7; page 19, lines 17 to page 21, line 4; and page 21, lines 19-25. For example, "with respect to the objects of the present invention, a non-producible protein is a protein that is difficult to express in eukaryotic host cells such as yeasts in recombinant production." *See* page 15, lines 2-10. Furthermore, the invention is useful for "proteins that cannot be recombinantly produced in both prokaryotic cells such as E. coli and eukaryotic cells such as yeasts, as well as a plurality of proteins that can be recombinantly produced in prokaryotic cells such as E. coli but are cost-ineffective due to their low yield in eukaryotic cells such as yeast." *See* page 15, lines 10-22.

Finally, the specification as filed provides many examples of non-producible proteins of the claimed invention. *See, e.g.*, page 19, line 17 to page 21, line 4; and Example 5 (*e.g.*, where the non-producible protein is human interleukin-2).

Thus, a person of ordinary skill in the art would be able to identify non-producible target proteins, *e.g.*, proteins which are poorly secreted by recombinant production, that could be used to identify a TFP using the claimed method.

It is believed that the claims as amended are clear and fully supported. Thus, it is respectfully requested that the Examiner reconsider and withdraw the 35 U.S.C. § 112 rejections.

6. Rejection under 35 U.S.C. § 102(b)

At page 10 of the Office Action, the Examiner has rejected claims 18-20, 22, 25, 28-33, and 38 as allegedly being anticipated under 35 U.S.C. § 102(b) by U.S. Patent No. 5,536,637, Jacobs et al. (hereafter '637). Applicants respectfully traverse this rejection.

Anticipation requires that all the elements and limitations of the claims are found, either explicitly or inherently, within a single reference. There must be no difference between the claimed invention and the reference disclosure as viewed by one of ordinary skill in the art. *Scripps Clinic & Research Fdn. V. Genentech*, 927 F.2d 1565, 1576 (Fed. Cir. 1991). Absence from a cited reference of any element of a claim negates anticipation of that claim by that reference. *Atlas Powder Co. v. E.I. Dupont de Nemours & Co.*, 224 U.S.P.Q. 409 (Fed. Cir. 1984). In the event that a reference does not explicitly teach all elements of a claim, anticipation can be shown by inherency if, and only if, the cited reference makes clear that the missing descriptive matter is *necessarily present* in the thing described in the reference. *Continental Can Co. USA Inc. v. Monsanto Co.*, 948 F.2d 1264 (Fed. Cir. 1991).

The '637 patent is relate to a method of screening for secreted mammalian proteins in which mammalian secretory leader sequences are detected using the yeast invertase gene as a reporter system. *See* '637 Abstract. In particular, '637 discloses a technique for selecting genes encoding signal sequence-containing (secreted) polypeptides. However, '637 fails to disclose part (a) of the current invention as presently claimed. In particular, '637 does not disclose preparing an automatic screening vector comprising a polynucleotide encoding a fusion polypeptide that comprises a non-producible target protein—as defined by the current specification—linked to a reporter protein.

An important distinguishing feature of the present invention is part (a) of claims 18 and 38. The current invention includes the preparation of an automatic screen vector in which a reporter gene is linked to a gene sequence encoding a non-producible target protein, such that secretion of the reporter protein from host cells is inhibited by fusion to the non-producible target protein. For example, this effect is disclosed on page 16, line 14-23 of the specification, which explains that when a non-producible target protein is fused to a reporter protein, such as invertase, the secretion of the reporter protein from host cells is significantly inhibited. Furthermore, a working example of (a) is disclosed in Example 2 (pages 43-46), which demonstrates that the expression of invertase was poor when fused to IL-2 (an example of a non-producible target protein).

In contrast, when cDNA fragments containing a leader sequence were fused to invertase in '637, invertase was efficiently secreted. That is, fusion of the cDNA fragments of '637 to a reporter protein (invertase) does not inhibit secretion of the reporter protein when fused thereto. Therefore, '637 do not disclose preparing an automatic screening vector comprising a polynucleotide encoding a non-producible target protein linked to a reporter protein as specified in (a) of amended claims 18 and 38.

Furthermore, the results achieved by the claimed invention differ from those disclosed in '637. In particular, secretion of the protein encoded by the reporter gene is inhibited by fusion to the non-producible target protein, and thus, the present invention provides a method capable of rapidly screening for a suitable translational fusion partner (TFP) *capable of inducing secretion of a non-producible target protein linked to a reporter protein.* In contrast, the method of '637 allow for the identification of signal sequences *capable inducing the secretion of a reporter protein.*

As discussed above, '637 fails to teach every limitation of claims 18 and 38 and furthermore this cited reference cannot anticipate claims 19-20, 22, 25, and 28-33, which depend ultimately therefrom. Therefore, it is respectfully requested that the rejection of claims 18-20, 22, 25, 28-33, and 38 under 35 U.S.C. § 102(b) as being anticipated by '637 be reconsidered and withdrawn.

7. Rejection under 35 U.S.C. § 103(a)

At pages 11-12 of the Office Action, the Examiner has rejected claims 18-20, 22-23, 25-34, and 38 under 35 U.S.C. § 103(a) as allegedly being obvious over '637; WO 99/49028, Baker et al.; and U.S. Patent 5,712,113, Chung et al. (hereafter '113). Applicants respectfully traverse this rejection.

In particular, the Examiner asserts that it would have been obvious because the substitution of one known element (i.e. genus of genomic DNA library, genus of promoter, and genus of secretion signals or fusion proteins as taught by WO 99/49028) for another (i.e. cDNA, genus of promoter, genus of secretion signals, genus of fusion polypeptides as taught by '637) for another (i.e. species of yeast gDNA library and species of Gal10 promoter taught by WO 99/49028 and species of human IL-2 and species of Gal10 promoter taught by '113) would have yielded predictable results (i.e. screening for secreted yeast polypeptides in yeast via an invertase reporter system utilizing TFP from a specific source, polypeptide expression on yeast via Gal10 promoter in vectors, etc.) to one of ordinary skill in the art at the time of the invention. Office Action, page 12. Applicants respectfully disagree.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki,* 745 F.2d 1468, 1471-73 (Fed. Cir. 1984). As set forth in *Graham v. John Deere Co. of Kansas*

City, "[u]nder § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined." 383 U.S. 1, 17 (1966). This has been the standard for over 40 years, and remains the law today. *See KSR Int'l. Co. v. Teleflex Inc.*, No. 04-1350, slip op. (2007). If, after these criteria are considered, the evidence indicates that the claimed invention is obvious over the prior art, it may be said that a *prima facie* case of obviousness have been established.

The Office has published Examination Guidelines to aid Examiners in formulating obviousness rejections. *See* MPEP § 2141 (hereinafter "the Examination Guidelines"). Seven rationales are suggested by which obviousness may be found, *e.g.*, by combining elements in the art or substituting one known element for another. As a common thread through all the rationales, the Examiner must establish on the record that a person of ordinary skill in the art would have recognized that the results of the combination or substitution were *predictable*. *Id.*

The Examiner has not met the burden of establishing a *prima facie* case of obviousness based on the Examination Guidelines. Specifically, the Examiner has not established that the ordinary artisan reading '637, WO 99/49028, and '113 would have predictably arrived at the presently claimed method of identifying TFPs.

The disclosure of '637 is discussed above. WO 99/49028 relates to a method of identifying cDNAs, which encode secreted and membrane-bound proteins by detecting their signal sequences using a reporter system. *See* WO99/49028, *e.g.*, at page 2, lines 28-30 and the Abstract. The method of WO99/49028 disclose vectors prepared by fusing an amylase gene lacking a functional signal sequence with cDNA libraries containing signal sequences. *See*

WO99/49028 at page 9, lines 34-36. However, WO99/49028 fails to disclose part (a) of the current invention as presently claimed.

'113 discloses secretion signal peptides of inulinase enzymes which cause heterologous proteins produced in yeast cells to be secreted almost completely out of the cell. Applicants respectfully point out that '113 does not disclose a screening method at all.

Thus, '637, WO 99/49028, and '113 fail to disclose a TFP screening method that includes preparing an automatic screening vector comprising a polynucleotide encoding a fusion polypeptide that comprises a non-producible target protein—as defined by the current specification—linked to a reporter protein as specified in (a) of amended claims 18 and 38. The combination of the cited documents does not predict all of the elements of the claimed invention. Thus, the documents cited by the Examiner cannot alone or in combination render the claimed invention obvious.

Because the cited references do not predict all of the limitations of the claims as amended, the claims are not rendered obvious and Applicants respectfully request that the rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

8. Provisional Obviousness-Type Double Patenting Rejection

At pages 9-10 of the Office Action, the Examiner has provisionally rejected claims 18-20, 22, 23, 25-34, and 38 as allegedly being unpatentable over claims 1-4, 11-17, 21-25, 33-35, 39-42, 45-47, 50-51, 54-55, 72, 74, 76-80, 86, 91, 97, 100, 105, 109, 114, 117, and 119 of U.S. Appl. No. 11/914,437 ("'437"). In particular, the Examiner indicates that although the claims are not identical, they are allegedly not distinct from each other because both the presently claimed methods and the methods as claimed in '437 are drawn to methods of identifying TFP.

Applicants respectfully traverse this provisional rejection for nonstatutory obviousness-type double patenting.

In particular, Applicants note that the '437 application is a National Stage Entry of PCT/IB2006/003102 filed on July 13, 2006, while the present application (10/586,045) is a National Stage Entry of PCT/KR04/03517 filed on December 30, 2004. According to the M.P.E.P:

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.

M.P.E.P. § 804.I.B.1

Thus, if the nonstatutory obviousness-type double patenting rejection over the '437 application is the only rejection remaining in the above-captioned application (*i.e.*, the "earlier filed of the two pending applications"), the double patenting rejection should be withdrawn without the need for a terminal disclaimer.

Applicants believe the above amendment and remarks address all other objections and rejections, which would thereby leave the provisional nonstatutory obviousness-type double patenting rejection over the '437 application as the only rejection remaining in the above-captioned application. Thus, Applicants respectfully request that the provisional obviousness-type double patenting rejection be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner

reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Eric K. Steffe
Attorney for Applicants
Registration No. 36,688

Date: 9/29/10

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

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